



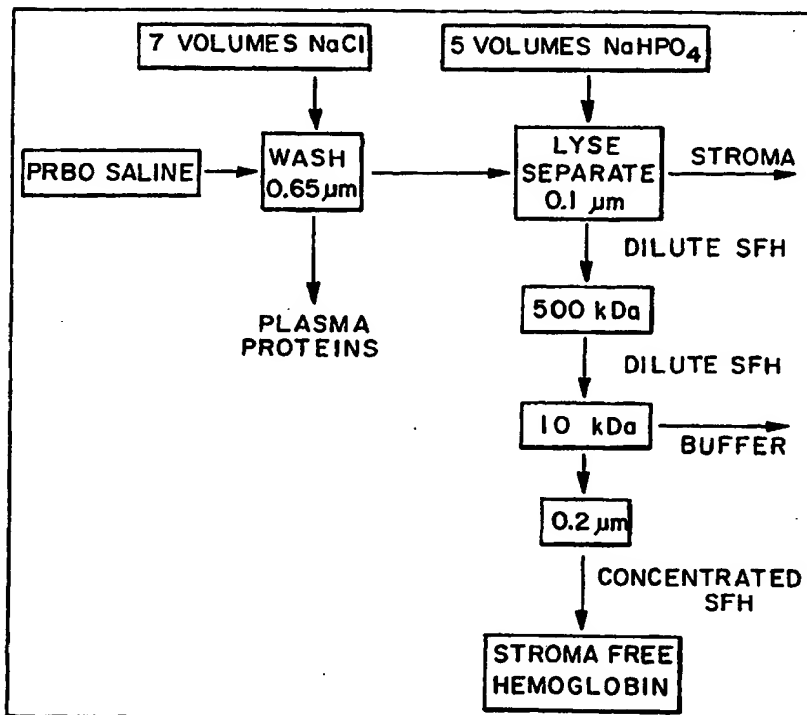
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61M 1/36		A1	(11) International Publication Number: WO 00/21591
			(43) International Publication Date: 20 April 2000 (20.04.00)
(21) International Application Number: PCT/US99/24149		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 15 October 1999 (15.10.99)		Published <i>With international search report.</i>	
(30) Priority Data: 60/104,319 15 October 1998 (15.10.98) US 60/122,180 1 March 1999 (01.03.99) US			
(71) Applicant (for all designated States except US): SANGART, INC. [US/US]; Suite L, 11199 Sorrento Valley Road, San Diego, CA 92121 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): WINSLOW, Robert, M. [US/US]; 1210 Inspiration Drive, La Jolla, CA 92037 (US). VANDEGRIFF, Kim, D. [US/US]; 311 Fourth Avenue #601, San Diego, CA 92101 (US).			
(74) Agents: MUSICK, Eleanor, M. et al.; Brown, Martin, Haller & McClain, 1660 Union Street, San Diego, CA 92101-2926 (US).			

(54) Title: METHOD FOR PRODUCTION OF STROMA-FREE HEMOGLOBIN

(57) Abstract

The method employs a commercially-available blood cell separator comprising a computer-controlled centrifuge (2) having a rotor (24) into which a blood processing bag (6) containing donor blood is placed. Once the blood is collected, the process is performed entirely within the enclosed centrifuge bowl, preferably in situ at the donor collection site. In the first step, the blood is centrifuged to separate the plasma from the cellular components. After isolation of the red blood cells from other blood components, the red cells are washed with normal saline or other solution. The red blood cells are then lysed by hypotonic shock to separate the red cell membranes (stroma) and the lysate is collected in a sterile container (44), leaving only the stroma in the centrifuge bowl. The final product can be used as raw material for any of the hemoglobin-based oxygen carriers currently being developed as red cell substitutes. All of the steps are performed within a processing container or blood bag (6) in the bowl centrifuge to minimize handling and maintain sterility. A method for preparing a modified hemoglobin solution incorporates the steps for producing stroma-free hemoglobin, then adding pre-measured reagents to react with the solution and filtering the solution.



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/24149

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 646 252 A (BERBERS WILHELMUS ANTONIUS ET AL) 8 July 1997 (1997-07-08) column 4, line 16 - line 67 column 9, line 35 - line 37	1,2,10, 14,15, 17,18
Y		3
A		7
Y	US 5 464 814 A (SEHGAL LAKSHMAN R ET AL) 7 November 1995 (1995-11-07) column 9, line 26 - line 41	3
X	EP 0 367 475 A (NIPPON OILS & FATS CO LTD) 9 May 1990 (1990-05-09) column 2, line 37 - line 39 column 3, line 10 - line 33	1,2,10, 11
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 January 2000

Date of mailing of the international search report

02/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lakkis, A

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/24149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 401 652 A (SIMMONDS RICHARD S ET AL) 30 August 1983 (1983-08-30)	10, 11, 14
	column 2, line 7 - line 68 column 3, line 50 - column 4, line 10	
A	-----	1, 2, 7, 12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/24149

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5646252 A	08-07-1997	NONE	
US 5464814 A	07-11-1995	US 4826811 A CA 1298783 A DE 3790322 C DE 3790322 T EP 0271542 A FR 2600255 A GB 2200639 A,B JP 1501471 T NL 8720283 A PT 85133 A,B WO 8707832 A US 5747649 A US 5194590 A	02-05-1989 14-04-1992 02-09-1999 15-09-1988 22-06-1988 24-12-1987 10-08-1988 25-05-1989 02-05-1988 01-07-1987 30-12-1987 05-05-1998 16-03-1993
EP 0367475 A	09-05-1990	JP 2121931 A CA 2000717 A CN 1042364 A	09-05-1990 29-04-1990 23-05-1990
US 4401652 A	30-08-1983	US 4469792 A	04-09-1984

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 7590-PCT01	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 24149	International filing date (day/month/year) 15/10/1999	(Earliest) Priority Date (day/month/year) 15/10/1998
Applicant SANGART, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

2

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/24149

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

The abstract is changed as follows:

Line 2: after "centrifuge" insert "(2)";
line 2: after "rotor" insert "(24)";
line 3: after "bag" insert "(6)";
line 9: after "container" insert "(44)";
line 13: after "bag" insert "(6)".

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/24149

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	✓ US 5 646 252 A (BERBERS WILHELMUS ANTONIUS ET AL) 8 July 1997 (1997-07-08) column 4, line 16 - line 67 column 9, line 35 - line 37	1,2,10, 14,15, 17,18
Y	---	3
A	---	7
Y	✓ US 5 464 814 A (SEHGAL LAKSHMAN R ET AL) 7 November 1995 (1995-11-07) column 9, line 26 - line 41	3
X	✓ EP 0 367 475 A (NIPPON OILS & FATS CO LTD) 9 May 1990 (1990-05-09) column 2, line 37 - line 39 column 3, line 10 - line 33 --- -/--	1,2,10, 11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 January 2000

Date of mailing of the international search report

02/02/2000

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lakkis, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/24149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 4 401 652 A (SIMMONDS RICHARD S ET AL) 30 August 1983 (1983-08-30) column 2, line 7 - line 68 column 3, line 50 -column 4, line 10 -----	10,11,14 1,2,7,12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/24149

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5646252	A	08-07-1997	NONE	
US 5464814	A	07-11-1995	US 4826811 A	02-05-1989
			CA 1298783 A	14-04-1992
			DE 3790322 C	02-09-1999
			DE 3790322 T	15-09-1988
			EP 0271542 A	22-06-1988
			FR 2600255 A	24-12-1987
			GB 2200639 A,B	10-08-1988
			JP 1501471 T	25-05-1989
			NL 8720283 A	02-05-1988
			PT 85133 A,B	01-07-1987
			WO 8707832 A	30-12-1987
			US 5747649 A	05-05-1998
			US 5194590 A	16-03-1993
EP 0367475	A	09-05-1990	JP 2121931 A	09-05-1990
			CA 2000717 A	29-04-1990
			CN 1042364 A	23-05-1990
US 4401652	A	30-08-1983	US 4469792 A	04-09-1984

PATENT COOPERATION TREATY

PCT

REC'D 28 SEP 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 7590-PCT01	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/24149	International filing date (day/month/year) 15 OCTOBER 1999	Priority date (day/month/year) 15 OCTOBER 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant SANGART, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

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Date of submission of the demand 17 MARCH 2000	Date of completion of this report 05 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer SUN UK KIM <i>[Signature]</i>
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0661

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/24149

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed☒ the description:

pages 1-18

pages NONE

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of

☒ the claims:

pages 19-21

pages NONE

pages NONE, as amended (together with any statement) under Article 19

pages NONE

pages NONE, filed with the demand

pages NONE, filed with the letter of

☒ the drawings:

pages 1-2

pages NONE

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of

☒ the sequence listing part of the description:

pages NONE

pages NONE

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig. NONE5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/24149

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims	<u>3-9, 12-13, 16</u>	YES
	Claims	<u>1-2, 10-11, 14-15, 17-18</u>	NO
Inventive Step (IS)	Claims	<u>6, 8-9, 13, 16</u>	YES
	Claims	<u>1-5, 7, 10-12, 14-15, 17-18</u>	NO
Industrial Applicability (IA)	Claims	<u>1-18</u>	YES
	Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-2, 14-15 and 17-18 lack novelty under PCT Article 33(2) as being anticipated by U.S. Patent No. 5,646,252 (hereinafter referred to as Berbers et al). Berbers et al teach a method of preparing hemoglobin solution comprising the steps of isolating red blood cells from blood by centrifuging, removing plasma from red blood cells, washing red blood cells with a normal saline solution, lysing red blood cells with water, dialyzing red blood cells to remove stromata and filtering red blood cells, collecting hemoglobin solutions in a container to react with a coupling agent and filtering and sterilizing reacted solution (see col. 4, lines 16-46; col. 7, line 48 - col. 8, line 4; col. 9, lines 5-37).

Claims 3-4 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of U.S. Patent No. 5,464,814 (hereinafter referred to as Sehgal et al). At best claims 3-4 differ from the method of Berbers et al in reciting washing solution comprising an agent for killing bacteria and/or inactivating virus. Sehgal et al teaches a method of preparing hemoglobin solution comprising the step of washing blood with saline solution containing antibiotics to provide hemoglobin solution free of bacteria and viruses (see col. 4, lines 21-34; col. 9, lines 25-49). It would have been obvious to add antibiotics in the wash solution of Berbers et al to kill bacteria and inactivate virus in blood to prepare hemoglobin solution free of bacteria and viruses.

Claims 1-2 and 10-11 lack novelty under PCT Article 33(2) as being anticipated by European Patent Application No. 367,475 (hereinafter referred to as EPA '475). EPA '475 teach a method of preparing hemoglobin solution comprising the steps of isolating red blood cells from blood by centrifuging, removing plasma from red blood cells, washing red blood cells with a normal saline solution, lysing red blood cells, centrifuging to remove membranes of red blood cells, dialyzing red blood cells to remove stromata and collecting hemoglobin solutions in a container (see col. 3, lines 10-39).
(Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/24149

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): B01D 21/26; A61M 1/36 and US Cl.: 210/645, 646, 650, 651, 739; 424/533; 435/2; 436/177, 178; 514/6; 530/385

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Claim 5 lacks an inventive step under PCT Article 33(3) as being obvious over EPA '475. EPA '475 teach a method of preparing hemoglobin solution as described in above paragraph. At best claim 5 differs from the method of EPA '475 in reciting that the processing steps are performed within a single processing container disposed within the centrifuge. It would have been obvious to consolidate all the processing steps in a single container in a centrifuge which are commonplace in the art of blood processing industry.

Claim 7 lacks an inventive step under PCT Article 33(3) as being obvious over EPA '475. EPA '475 teach a method of preparing hemoglobin solution as described in above paragraph. At best claim 7 differs from the method of EPA '475 in reciting the use of a sterile processing set comprising a processing bag and a tube harness in a centrifuge. A sterile processing set comprising a processing bag and a tube harness in a centrifuge is common blood processing centrifuge equipment. It would have been obvious to use a well-known blood processing bags in a centrifuge to aid in preparation of hemoglobin solutions from blood.

Claim 12 lacks an inventive step under PCT Article 33(3) as being obvious over EPA '475 and further in view of U.S. Patent No. 5,464,814 (Sehgal et al). At best claim 12 differs from the method of Berbers et al in reciting the step of adding a detergent, antibacterial or antiviral agent to the saline solution. Sehgal et al teaches a method of preparing hemoglobin solution comprising the step of washing blood with saline solution containing antibiotics to provide hemoglobin solution free of bacteria and viruses (see col. 4, lines 21-34; col. 9, lines 25-49). It would have been obvious to add antibiotics in the saline solution of EPA '475 to kill bacteria and inactivate virus in blood to prepare hemoglobin solution free of bacteria and viruses.

Claims 6, 8-9, 13 and 16 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claims 6, 8-9 and 13 comprising a step of measuring an ionic concentration of the hemolysate or hemoglobin solution and removing or extracting hemoglobin until the ionic concentration decreases to a predetermined level, and the buffer salts of claim 16 comprising iminothiolane and activated polyethylene glycol.

Claims 1-18 have industrial applicability as defined by PCT Article 33(4) because claimed subject matter can be made and/or used in the blood processing industry.

----- NEW CITATIONS -----
NONE

ATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

BROWN, MARTIN, HALLER & McCLAIN
Attn. MUSICK, Eleanor M.
1660 Union Street
San Diego, CA 92101-2926
UNITED STATES OF AMERICA

Response due: Apr. 2, 2000

Date of mailing
(day/month/year)

02/02/2000

Applicant's or agent's file reference

7590-PCT01

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 99/24149

International filing date
(day/month/year)

15/10/1999

Applicant

SANGART, INC. et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2

Authorized officer

Robert Berends

51 epo nl,

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/24149

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 646 252 A (BERBERS WILHELMUS ANTONIUS ET AL) 8 July 1997 (1997-07-08) column 4, line 16 - line 67 column 9, line 35 - line 37	1,2,10, 14,15, 17,18
Y A	-----	3 7
Y	US 5 464 814 A (SEHGAL LAKSHMAN R ET AL) 7 November 1995 (1995-11-07) column 9, line 26 - line 41 -----	3
X	EP 0 367 475 A (NIPPON OILS & FATS CO LTD) 9 May 1990 (1990-05-09) column 2, line 37 - line 39 column 3, line 10 - line 33 -----	1,2,10, 11
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 January 2000

Date of mailing of the international search report

02/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Lakkis, A

INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/US 99/24149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 401 652 A (SIMMONDS RICHARD S ET AL)	
	30 August 1983 (1983-08-30)	10, 11, 14
	column 2, line 7 - line 68	
A	column 3, line 50 - column 4, line 10	
	-----	1, 2, 7, 12

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2000 (15.05.00)	
International application No. PCT/US99/24149	Applicant's or agent's file reference 7590-PCT01
International filing date (day/month/year) 15 October 1999 (15.10.99)	Priority date (day/month/year) 15 October 1998 (15.10.98)
Applicant WINSLOW, Robert, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

17 March 2000 (17.03.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
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